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Neural Tube Defects and Deletions of 22q11

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Recently we reported on three unrelated children with neural tube defects (NTDs) and deletion of 22q11. Two of these children have velo-cardio-facial syndrome and the third DiGeorge sequence. Thus, NTDs appear to be part of the clinical picture due to 22q11 deletion. To further explore this association and to clarify what findings should prompt testing for this deletion in individuals with NTDs, we have reviewed all patients in a large regional spina bifida clinic population.

Two hundred ninety-five patients with NTDs were identified by chart review. Charts were reviewed for congenital heart defect, minor facial anomalies, thymic hypoplasia, cleft lip and/or palate, hypocalcemia, and a family history of a NTD, congenital heart defect, or cleft lip and/or palate. A total of 22 patients was identified with NTD and at least one more clinical trait and/or a positive family history. Sixteen children received cytogenetic and molecular testing including the three previously reported patients diagnosed with a 22q11 deletion. Results of cytogenetic and molecular studies of the remaining 13 patients were normal.

Deletion of 22q11 is an infrequent cause of NTDs. We recommend testing for the 22q11 deletion in patients with a NTD and conotruncal heart defect. Testing should be considered in patients with a NTD who have a first degree relative with a conotruncal heart defect or have additional clinical findings of VCFS or DGS.

KEY WORDS: neural tube defect, meningomyelocele, cleft palate, congenital heart defect, conotruncal heart defect, deletion 22q11, velo-cardio-facial syndrome, DiGeorge sequence

INTRODUCTION

Most individuals with velo-cardio-facial syndrome (VCFS) and DiGeorge sequence (DGS) and many patients with nonsyndromic congenital conotruncal heart defects have a del(22)(q11). Recent studies have shown del(22)(q11) in as many as 88% of patients with DGS [Driscoll et al., 1993], 76% of patients with VCFS [Driscoll et al., 1993], and 29% of patients with nonsyndromic conotruncal heart defects [Goldmuntz et al., 1993].

Recently we reported on three unrelated children with neural tube defects (NTDs) associated with del(22)(q11) [Nickel et al., 1994]. Two of these children have VCFS and the third DGS. All three have lumbosacral or sacral meningomyelocele and conotruncal heart defects. The two children with VCFS also have bifid uvula. Therefore, NTDs appear to be part of the variable clinical picture due to 22q11 deletion. We have reviewed all patients in a large regional spina bifida clinic population to further explore this relationship and to provide guidelines for testing children with NTDs for the 22q11 deletion.

METHODS

We reviewed the charts of all active and inactive patients of the Spina Bifida Clinic at the Child Development and Rehabilitation Center, Oregon Health Sciences University. We included in the study all patients who had a congenital cardiac defect (CHD); minor facial anomalies, thymic hypoplasia, cleft lip and/or palate (CL/P), and hypocalcemia, or a family history in a first degree relative of a NTD, CHD, or CL/P. Individuals with sacral agenesis, a known chromosome anomaly, or a definite syndromic diagnosis were excluded. The presence of a learning disability was not used as a trait since most individuals with spina bifida have a learning disability.

Patients were rated as having minor facial anomalies if any of the following were noted in the chart: a wide and flat nasal bridge, short palpebral fissures, prominent nasal root, malar hypoplasia, low-set and posteriorly angulated ears, round ears, small mouth or "facial dysmorphic features." The patients identified by the chart review were scheduled for examination in the Spina Bifida Clinic and offered high resolution cytogenetic testing and deletion analysis with fluorescence in situ hybridization (FISH) with the probes for two mark-

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ers in the DiGeorge chromosome region (DGCR) N25 [Driscoll et al., 1992] and D0835 [Wadey et al., 1993].

RESULTS

Two hundred ninety-five patients with NTDs were identified. The three patients with NTDs and deletion of 22q11 who were reported previously were included in this study. The number of individuals noted having one or more of the study traits in addition to the NTD are presented in Table I; 22 such patients were identified.

Ten patients (3.4%) had a congenital heart defect including nine with conotruncal defects (three with tetralogy of Fallot, and one with Type B interrupted aortic arch). Eight children (2.6%) had minor anomalies. Three patients with fetal alcohol syndrome and one patient with fetal valproate syndrome were excluded from the study. These four children did not have a CHD, CL/P, or any other anomaly in addition to the NTD and minor facial anomalies. Nine children (3.0%) had CL/P including six patients with bifid uvula or cleft palate only. Four patients had a positive family history, including three children with a sib with a NTD and one child with a brother who died during surgery for a CHD.

Twenty-one of the twenty-two children were examined. One child and family were unable to return for the exam. That child has a ventricular septal defect with aortic insufficiency, vertebral anomalies with a lumbar syringomyelia, and a brother with a CHD. The clinical diagnosis of possible VCFS was made after review of her photographs by both authors. The two children with VCFS and the child with DGS reported on previously had multiple clinical findings characteristic of these syndromes [Nickel et al., 1994]. The physical findings did not support a clinical diagnosis of VCFS or DGS in any of the other patients.

The results of cytogenetic analysis and molecular testing on 16 children and their manifestations are presented in Table II. Six families refused testing. A high-resolution cytogenetic study (700–750 band level) on one of the three children reported on previously demonstrated an interstitial deletion [del (22) (q11-21.23)]. All three of these children had deletions of 22q11 at locus D22S75 demonstrated by dosage analysis or by fluorescence in situ hybridization studies (FISH). Cytogenetic analysis and molecular studies were normal in the remainder of the children. The findings of the six children who were not tested included three children with NTD and CHD (one ventricular septal defect, one mild valvular pulmonary stenosis, and one ventriculoseptal defect with mild tricuspid insufficiency); one child with a NTD, bifid uvula, and tracheoesophageal fistula/esophageal atresia; one child with a NTD and minor anomalies, and one child with a NTD, cerebellar aplasia, unilateral cleft lip and palate, and minor facial anomalies. The physical findings did not support the diagnosis of VCFS or DGS in any of these six children.

DISCUSSION

Approximately 5% of the children with NTDs have an associated congenital heart defect or cleft lip and/or palate [Brown, 1975]. These children should have further evaluation to determine a possible chromosomal, teratogenic, or genetic cause for this combination, for example, trisomy 18, fetal valproate syndrome, or deletion of 22q11. Recent studies have demonstrated that the clinical picture of deletion 22q11 is highly variable [Chow et al., 1994; Driscoll et al., 1993; Goldberg et al., 1993; Goldmuntz et al., 1993; Matsuoka et al., 1994; Wilson et al., 1993] and includes congenital heart defect, cleft palate, and NTD [Nickel et al., 1994].

Ten children in our study had congenital cardiac defects (3.4%). In a previous report, 10 of 434 children (2.3%) with meningomyelocele had congenital heart defects [Brown, 1975]. This includes three children with tetralogy of Fallot and one child with Type B interrupted aortic arch with aberrant subclavian artery and a ventricular septal defect. These are the cardiac defects typically associated with VCFS and DGS, respectively [Young et al., 1980; Lodewyk et al., 1986]. We did not differentiate conoventricular septal defects from other types of VSD since this information was not available on all patients. Conoventricular septal defects are highly associated with deletion of 22q11 in the absent pulmonary valve syndrome [Johnson et al., 1995]. Nine children in our study had cleft lip and/or palate (3.0%). This includes six children with bifid uvula or cleft palate only (2.0%). Six of 434 patients (1.4%) in a previous report had cleft lip and/or palate and five of the 434 children had cleft palate or bifid uvula only [Brown, 1975].

Deletion of 22q11 appears to be an infrequent cause of NTDs. There has been a single case report of meningomyelocele in association with DGS, although cytogenetic and molecular studies were not reported [Palacios et al., 1993]. Previously we reported on three children with NTDs and deletions of 22q11 and in this study made the clinical diagnosis of possible VCFS in

TABLE I. Number of Patients With a NTD and Each Additional Study

Congenital heart defect (CHD)	10	Nine patients had conotruncal heart defects, including three with tetralogy of Fallot
Minor facial anomalies (AbF)	8	
Thymic hypoplasia (T)	1	The child with DGS
Cleft lip and/or palate (CL/P)	9	Six patients had bifid uvula or cleft palate only
Hypocalcemia (H)	1	The child with DGS
Family history of NTD, CL/P, CHD	4	Three siblings had a NTD, one had a CHD (VSD)

TABLE II. Results of Cytogenetic Testing and Deletion

Study traits[a]	Number of children	Clinical diagnosis	22q11 Deletion
NTD, CHD, AbF, T	1	1 DGS	1
NTD, CHD, AbF, CL/P	2	2 VCFS	2
NTD, CL/P, FHx (1)	1		0
NTD, CL/P, AbF (2)	2		0
NTD, CHD	2	1 VCFS?	0
NTD, CL/P	4		0
NTD, AbF	1		0
NTD, FHx	3		0
Total	16		3

[a]NTD, neural tube defect; CHD, congenital heart defect; AbF, abnormal face; T, thymic hypoplasia; CL/P, cleft lip and/or plate; H, hypocalcemia; and FHx, "positive" family history.

an additional child. The diagnosis of VCFS in this child will be reviewed when she returns for clinic follow-up later this year. The number of children with the 22q11 deletion in our clinic may be larger since patients in our study were identified by chart review. The quality of information, particularly for the family history and for facial appearance, varied considerably from chart to chart. Six families refused cytogenetic and molecular testing.

Which patients with NTDs should be tested for the 22q11 deletion? Previously we recommended testing all children with a NTD and congenital heart defect, a NTD and cleft palate, or a NTD and facial anomalies compatible with VCFS and DGS [Nickel et al., 1994]. Our current recommendations are to test any patient with a NTD and conotruncal heart defect. Three of the four children with heart defects typical of VCFS or DGS (tetralogy of Fallot or Type B interrupted aortic arch) had deletions of 22q11. However, none of the patients with a NTD and VSD alone were deleted. In addition, testing should be considered in patients with a NTD who have a first degree relative with a conotruncal heart defect, or have additional clinical findings that strongly support a diagnosis of VCFS or DGS.

These recommendations should continue to be viewed as preliminary until further studies of the 22q11 deletion in individuals with NTDs are completed. Patients with NTDs and deletions of 22q11 appear to represent the most severe end of the clinical spectrum for this deletion. The similar clinical manifestations of DGS and VCFS may represent a contiguous gene deletion syndrome [Motzkin et al., 1993]. In the future, further characterization of the genes and DNA sequences deleted may allow accurate prediction of the spectrum of clinical problems for affected patients and may contribute to understanding the mechanism(s) of neural tube closure.

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